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Klinikinė praktika

Ovarian Dysgerminoma with Metastases in Supraclavicular Lymph Nodes Diagnosed in a 16-year-old Girl: Clinical Case and Literature Review

Kiaušidės disgerminoma su metastazėmis viršraktikauliniuose limfmazgiuose, diagnozuota 16 metų merginai: klinikinis atvejis ir literatūros apžvalga

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Background

Tumors of children reproductive system are rare, the most frequent among them is ovarian tumor. The most frequent histological type of ovarian tumor in girls and adolescents is germ cell tumor, with dysgerminoma being the most frequent of all. Symptoms are very non-specific, this is why these tumors are often diagnosed late. Dysgerminoma is a malignant tumor, thus if not treated, it may be potentially lethal.

Case report

We present a 16-year old patient, who has come to Vilnius University Hospital Santaros Klinikos, Children's unit, due to a sudden emergence of a growth above the left clavicle. The girl did not have any other specific complaints. Huge hard growth was founded during palpation of the abdomen. After the cancer marker test (alfa-fetoprotein – 1,9 kU/L, beta-human chorionic gonadotropin – 1231.0 U/L; lactate dehydrogenase – 2721.0 U/L; Ca125 – 665.8 kU/L), pelvic ultrasound examination, computed tomography and histological evaluation of the supraclavicular mass, dysgerminoma of the right ovary FIGO stage IV was diagnosed. The patient was treated with laparotomic oophorectomy and chemotherapy before and after surgery. Treatment was successful as 100% of tumor cells necrosis was achieved.

Conclusions

Girls and adolescents should be suspect to ovarian masses if they complains about abdominal pain, a growth in the abdominal area, disruptions of menstrual cycle or signs of premature puberty. Early diagnosis and treatment of ovarian dysgerminoma have a very good recovery rate in girls and adolescent.

Key words: ovarian tumors in girls and adolescents, malignant germ cell tumors, dysgerminoma, nonepithelial tumors.

Įvadas

Vaikų reprodukcinės sistemos navikai yra reti, būdingiausias iš jų – kiaušidžių navikas. Germinogeniniai navikai – dominuojantis mergaičių, ypač paauglių, kiaušidžių navikų histologinis tipas. Iš šių navikų dažniausia disgerminoma. Simptomai labai nespecifiniai, todėl navikai diagnozuojami vėlai. Disgerminoma – piktybinis navikas, todėl negydant prognozė gali būti letali.

Atvejo aprašymas

Į Vilniaus universiteto ligoninės Santaros klinikų Vaikų ligoninės priėmimo skyrių kreipėsi 16 m. pacientė dėl kairėje viršraktikaulinėje srityje staiga atsiradusio darinio. Kitų specifinių skundų mergina neturėjo. Čiuopiant pilvą aptiktas didelis kietas darinys. Atlikus vėžio žymenų tyrimus (alfa fetoproteinas – 1,9 kU/L, beta chorioninis gonadotropinas – 1231,0 U/L; lakatato dehidrogenazė – 2721,0 U/L; Ca125 – 665,8 kU/L), dubens organų ultragarsą, kompiuterinę tomografiją ir viršraktikaulinio darinio histologinį tyrimą, pacientei diagnozuota FIGO IV stadijos dešinės kiaušidės disgerminoma. Pacientei prieš operacinį gydymą ir po jo buvo atlikta laparotominė ovarektomija ir chemoterapija. Gydymas buvo sėkmingas – rasta 100 proc. naviko ląstelių nekrozė.

Išvados

Mergaitėms, ypač paauglėms, gali būti įtartas kiaušidžių darinys, jei skundžiamasi pilvo skausmu, dariniu pilve, nereguliariu mėnesinių ciklu ar ankstyva branda. Ankstyva mergaičių, ypač paauglių, disgerminomų diagnostika ir gydymas lemia labai gerą šių navikų prognozę.

Reikšminiai žodžiai: mergaičių, ypač paauglių, kiaušidžių navikai, piktybiniai germinogeniniai navikai, disgerminoma, neepiteliniai navikai.

Introduction

Tumors of children reproductive system are rare [1], the most frequent among them is ovarian tumor [2]. About half of all ovarian masses founded in juvenile and adolescent girls are neoplastic [1, 3, 4]. It accounts for 2.6/100 000 cases every year [5]. Approximately 10–20% of all neoplastic masses are malignant [1–4, 6–14]. Malignant ovarian tumors constitute 1–2 percent of all children's malignant tumor cases and 3% of girl's malignant tumor cases [2, 4, 7–10, 12]. Unlike adult females, juvenile and adolescent girls often have tumors of non-epithelial origin [2], they comprise as much as 80% of all tumors [2, 8, 9]. The most frequent among them are germ cell ovarian tumors (60–80% of all non-epithelial ovarian tumors) [1, 2, 4, 8, 14]. Young girls with ovarian tumors generally have a better survival rate than older women [2]. The 5 year overall survival (OS) of patients with malignant tumors of all stages is 98.5% (95% confidence interval (CI): 95.6–100%), 5 year event free survival (EFS) is 84.5% (95% CI: 76.5–93.5%) [16]. The survival of patients with early

stages of malignant tumors after surgery and adjuvant chemotherapy (with platinum) is 90% [13]. The 5 year survival of patients with the first stage tumors is 95.6%, with advanced stage tumors – 73.2%, total survival rate (all tumors) is 89.4% [2].

Case report

16 year old patient arrived to Santaros Klinikos of Vilnius University Hospital, Children's unit, with a sudden formation above the left clavicle. The girl complained about frequent defecation (1–2 times daily), weight loss (9 kg per 2 months), dry cough (for about 1 month), and general weakness (for about 2 weeks). The examination results were as follows: pale skin, visible and palpable, painless and immobile formation above the left clavicle (4x4 cm). The patient was coughing irritably, vesicular breathing pattern on both chest sides was heard during the auscultation, and there was no crepitation. There was a visible abdominal asymmetry, and a palpable, large (30x30x35 cm) and hard formation in the abdomen, slightly on the right

side. Laboratory test results showed: alfa-fetoprotein (AFP) – 1,9 kU/L, beta-human chorionic gonadotropin (beta-hCG) – 1231.0 U/L; lactate dehydrogenase (LDH) – 2721.0 U/L; Ca125 – 665.8 kU/L. Liver and kidney function was normal, C reactive protein (CRP) was 54,6 mg/L. Pelvic ultrasound (US) examination showed a large (46x28x18 cm), solid, heterogeneous (with liquid spaces and calcinates) formation, growing out of the right ovary, and free fluid inside the abdomen. Computed tomography (CT) was used to verify the US examination findings, the results were as follows: supraclavicular pathological masses, pathological masses in the posterior mediastinum, bilateral pleurisy and fluid in the pleural space; pathological formation in the abdomen and pelvis: it's size was 27.24x25.51x13.25 cm, the tumor was lobulated, consisting of two big nodes, it had necrotic zones and calcinates; hepatosplenomegaly; free fluid in the abdominal cavity. Germ cell ovarian tumor with metastases in the supraclavicular lymph nodes was suspected. Following a biopsy of the supraclavicular lymph nodes, the suspicion was confirmed. No metastases were found in the bone marrow. The patient was diagnosed with dysgerminoma of the right ovary FIGO stage IV. The patient was prescribed chemotherapy treatment – three cycles of BEP (cisplatin / etoposide / bleomycin). Later beta-hCG, LDH and Ca125 decreased till 5.9 U/L, 418.0 U/L and 169.9 U/L, respectively. CT also was repeated after chemotherapy: there were no pathological masses left in the left supraclavicular area; the ovarian tumor and lymph nodes conglomerates in the posterior mediastinum and the retroperitoneal space showed a partial response to the treatment – 50% reduction; hepatosplenomegaly persists; pleural and abdominal cavity fluids were no longer present. The decision was made to operate the patient. During the laparotomy, the right ovary and the affected part of the right fallopian tube were removed. The hardened and enlarged para-aortic lymph nodes of the retroperitoneal space were removed as well. Results of the histological examination showed: dysgerminoma of the right ovary; metastases of dysgerminoma in the supraclavicular lymph nodes; full post-therapeutic regression of ovarian dysgerminoma and metastases in the supraclavicular lymph nodes: 100% post-therapeutic cell necrosis and fibrosis. An immunohistochemical examination showed

that 100% of the tumor cells were positive for CD117 and Salla4 markers. The 4th chemotherapy course was applied after the laparatomic oophorectomy. Then CT was repeated, and it showed active lymph nodes conglomerate, therefore it was decided to do relaparotomy. The para-aortic nodes of the retroperitoneal space were removed; histology showed necrotized cells of dysgerminoma metastases. The patient's five months duration treatment was successfully completed; long term follow-up was applied to prevent potential relapse.

Discussion

In 2014 the World Health Organization (WHO) announced the new histological classification of ovarian tumors. In this classification, superficial epithelial ovarian tumors are classified into serous, mucinous, endometrioid, clear cell, Brenner, seromucinous, undifferentiated, mesenchymal and mixed epithelial-mesenchymal tumors. Non epithelial tumors are divided into sex cord-stromal and germ cell tumors. Among all histological types of tumors, benign, borderline or malignant tumors are present [15]. Germ cell ovarian tumors are most commonly diagnosed in the first two decades of life, averagely at 16–20 years [16]. They account for as much as 70% of all ovarian tumors in women aged 10–30 years [1, 2, 4, 14]. 20–30% of germ cell tumors are malignant and represent 1–3% of all ovarian malignant tumors [4, 16, 17]. Malignant germ cell tumors include immature teratomas, dysgerminomas, yolk sac tumors, embryonic tumors, choriocarcinomas, poliembriomas and mixed tumors. Other rare malignant germinal tumors belong to the heterogeneous tumor group [18, 19]. Immature teratomas, dysgerminomas, yolk sac tumors and mixed tumors account for 90% of all germ cell tumors (dysgerminomas are the most common ones, 34% cases, immature teratomas make up 30% cases) [2, 16, 17]. Germ cell tumors are usually one-sided, discovered in the first stage and are susceptible to chemotherapy [2, 3, 6, 7, 9], their prognosis is very good [1.9]. 5 year OS is >95%, the best survival rate is in case of dysgerminoma, the worst one is in case of immature teratomas, yolk sac tumors and mixed tumors [17].

Clinical diagnosis of ovarian tumors consists of clinic, cancer markers, US, CT/MRI (magnetic resonance imaging) and intraoperative data. The final diagnosis

of tumor is determined only after the findings of the histological examination [17–21]. Ovarian tumor is differentiated from the primary neoplastic and non-neoplastic pathology of other organs (not ovaries). It should be kept in mind that ovaries may have secondary malignant tumors – i.e. metastases of tumors of other organs [18]. Ovarian tumors are usually asymptomatic in the early stages and are therefore diagnosed late. The most common symptom of ovarian tumors is abdominal pain. It can be accompanied by dyspepsia and disorders of urination or defecation. Menstrual disorders, signs of premature puberty or virilization are common. The tumor can be discovered by performing a bimanual examination *via* the rectum, vagina or abdominal wall. Cancer markers typical for dysgerminomas are: AFP, beta-hCG, LDH, Ca125 [17–21]. Ovarian masses are diagnosed with transabdominal and transvaginal pelvic ultrasonography [17–21]. CT and / or MRI with contrast are used for differential diagnosis and appropriate staging [4, 17, 20]. Dysgerminomas are large, solid, lobulated, hyper / neo-vascularized tumors of varied echogenicity. Multiplicity, septations and compartments of the tumor are common [22, 23]. Tumor cells are positive for Salla4, OCT3/4 and CD117 markers during an immunohistochemistry examination. In the future, these markers can be used for treatment with target therapy [18, 24, 25].

Gonadal dysgenesis is a risk factor for germ cell ovarian tumors. Gonadoblastoma is a rare sex cord-stromal tumor. A pure gonadoblastoma is a benign tumor, but in 50–60% of cases it contains malignant germinal tumor cells [17], most frequently it is dysgerminoma [26, 27]. Gonadoblastoma is most often associated with gonadal dysgenesis [1]. Mutations of 12p chromosome and c-kit gene in 4q chromosome are found in >80% of dysgerminoma cases. It is thought that the mutation of

kit gene leads to development of more malignant tumor. It has been observed that the amplification of kit gene is directly related to the expression of the KIT protein in tumor cells [28, 29].

Surgery and chemotherapy are used to treat malignant ovarian tumors in girls and adolescents. The aim of the treatment is to leave as much of the healthy ovarian tissue as possible without compromising the radicality of the treatment, since about 20% of cases are characterized by metachronous tumors in contralateral ovary [1, 6–9]. Laparotomic oophorectomy is the first-line treatment for the elimination of children's malignant tumors [7, 21]. During the operation a partial surgical staging is performed. The stage of the tumor is established according the FIGO classification [18, 19]. After the surgery adjuvant chemotherapy is prescribed to all patients except those with IA or IB dysgerminomas. First-line choice is 3/4 cycles of PEB (cisplatin / etoposide / bleomycin). The neoadjuvant chemotherapy may also be applied, when tumor is inoperable. After the treatment the patient should be monitored for a long time (at least 5 years) due to the potential for recurrence [13, 16, 18].

Conclusions

Malignant ovarian tumors in girls and adolescent is very rare pathology, however, if not treated, it may be potentially lethal. The most frequent tumors in this particular age group are the tumors of germ cells – dysgerminomas. Symptoms are very non-specific, this is why these tumors are often diagnosed late. Juvenile or teenage girl's complains about abdominal pain, a growth in the abdominal area, disruptions of menstrual cycle or signs of premature puberty, should rise a suspicion of ovarian tumor. Early diagnosis and treatment have a very good recovery rate [30, 31].

REFERENCES

1. Taskinen S, Fagerholm R, Lohi J, Taskinen M. Pediatric ovarian neoplastic tumors: incidence, age at presentation, tumor markers and outcome. *Acta Obstet Gynecol Scand.* 2015 Apr; 94(4): 425–429.
2. Baert T, Storme N, Van Nieuwenhuysen E, Uyttebroeck A, Van Damme N, Vergote I, Coosemans A. Ovarian cancer in children and adolescents: A rare disease that needs more attention. *Maturitas* 2016 Jun; 88: 3–8.
3. Spinelli C, Pucci V, Buti I, Liserre J, Messineo A, Bianco F, Ugolini C. The role of tumor markers in the surgical approach of ovarian masses in pediatric age: a 10-year study and a literature review. *Ann Surg Oncol.* 2012 Jun; 19(6): 1766–1773.
4. Spinelli C, Strambi S, Liloia C, Bertocchini A, Messineo A. Update on the surgical management of ovarian neoplasms in children and adolescents: analysis on 32 cases. *Gynecol Endocrinol.* 2016 Oct; 32(10): 787–791.

5. Pfeifer SM, Gosman GG. Evaluation of adnexal masses in adolescents. *Pediatr Clin N Am* 1999; 46: 573–592.
6. Madenci AL, Levine BS, Laufer MR, Boyd TK, Voss SD, Zurakowski D, Frazier AL, Weldon CB. Preoperative risk stratification of children with ovarian tumors. *J Pediatr Surg*. 2016 Sep; 51(9): 1507–1512.
7. Papic JC, Finnell SM, Slaven JE, Billmire DF, Rescorla FJ, Leys CM. Predictors of ovarian malignancy in children: overcoming clinical barriers of ovarian preservation. *J Pediatr Surg*. 2014 Jan; 49(1): 144–147; discussion 147–148.
8. Hermans AJ, Kluivers KB, Wijnen MH, Bulten J, Massuger LF, Coppus SF. Diagnosis and treatment of adnexal masses in children and adolescents. *Obstet Gynecol*. 2015 Mar; 125(3): 611–615.
9. Péroux E, Franchi-Abella S, Sainte-Croix D, Canale S, Gauthier F, Martelli H, Pariente D, Adamsbaum C. Ovarian tumors in children and adolescents: a series of 41 cases. *Diagn Interv Imaging*. 2015 Mar; 96(3): 273–282.
10. Abbas PI, Elder SC, Mehollin-Ray AR, Braverman RM, Lopez ME, Francis JA, Dietrich JE. Ovarian lesion volumes as a screening tool for malignancy in adolescent ovarian tumors. *J Pediatr Surg*. 2015 Nov; 50(11): 1933–1936.
11. Marro A, Allen LM, Kives SL, Moineddin R, Chavhan GB. Simulated impact of pelvic MRI in treatment planning for pediatric adnexal masses. *Pediatr Radiol*. 2016 Aug; 46(9): 1249–1257.
12. Hayes-Jordan A, Lopez C, Green HL, Xiao LC, Huh W, Herzog CE. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric ovarian tumors: a novel treatment approach. *Pediatr Surg Int*. 2016 Jan; 32(1): 71–73.
13. Billmire DF, Cullen JW, Rescorla FJ, Davis M, Schlatter MG, Olson TA, Malogolowkin MH, Pashankar F, Villaluna D, Krailo M, Egler RA, Rodriguez-Galindo C, Frazier AL. Surveillance after initial surgery for pediatric and adolescent girls with stage I ovarian germ cell tumors: report from the Children's Oncology Group. *J Clin Oncol*. 2014 Feb 10; 32(5): 465–470.
14. Azarakhsh N, Grimes S, Chotai PN, Shephard C, Huang EY. Post-resection outcomes for pediatric ovarian neoplasm: is ovarian-preserving surgery a good option? *Pediatr Surg Int*. 2017 Jan; 33(1): 97–104.
15. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. 4th Revised ed. International Agency for Research on Cancer, 2014.
16. Terenziani M, Bisogno G, Bolchini R, Cecchetto G, Conte M, Boschetti L, De Pasquale MD, Biondi D, Inserra A, Siracusa F, Basso ME, De Leonardis F, Di Pinto D, Barretta F, Spreafico F, D'Angelo P. Malignant ovarian germ cell tumors in pediatric patients: The AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) study. *Pediatr Blood Cancer*. 2017 Nov; 64(11).
17. Kelleher CM, Goldstein AM. Adnexal masses in children and adolescents. *Clin Obstet Gynecol*. 2015 Mar; 58(1): 76–92.
18. National Comprehensive Cancer Network. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer (version 1.2017). Available at: <https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf>.
19. Colombo N, Peiretti M, Garbi A, Carinelli S, Marini C, Sessa C; ESMO Guidelines Working Group. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012 Oct; 23 Suppl7: vii20–6.
20. Cartault A, Caula-Legriel S, Baunin C, Le Mandat A, Lemasson F, Galinier P, Pienkowski C. Ovarian masses in adolescent girls. *Endocr Dev*. 2012; 22: 194–207.
21. Amies Oelschlager AM, Gow KW, Morse CB, Lara-Torre E. Management of Large Ovarian Neoplasms in Pediatric and Adolescent Females. *J Pediatr Adolesc Gynecol*. 2016 Apr; 29(2): 88–94.
22. Tsuboyama T, Hori Y, Hori M, Onishi H, Tatsumi M, Sakane M, Ota T, Tomiyama N. Imaging findings of ovarian dysgerminoma with emphasis on multiplicity and vascular architecture: pathogenic implications. *Abdom Radiol (NY)*. 2018 Feb 15.
23. Guerriero S, Testa AC, Timmerman D, Van Holsbeke C, Ajossa S, Fischerova D, Franchi D, Leone FP, Domali E, Alcazar JL, Parodo G, Mascilini F, Virgilio B, Demidov VN, Lipatenkova J, Valentin L. Imaging of gynecological disease (6): clinical and ultrasound characteristics of ovarian dysgerminoma. *Ultrasound Obstet Gynecol*. 2011 May; 37(5): 596–602.
24. Cheng L, Thomas A, Roth LM, Zheng W, Michael H, Karim FW. OCT4: a novel biomarker for dysgerminoma of the ovary. *Am J Surg Pathol*. 2004 Oct; 28(10): 1341–1346.
25. Sever M, Jones TD, Roth LM, Karim FW, Zheng W, Michael H, Hattab EM, Emerson RE, Baldrige LA, Cheng L. Expression of CD117 (c-kit) receptor in dysgerminoma of the ovary: diagnostic and therapeutic implications. *Mod Pathol*. 2005 Nov; 18(11): 1411–1416.
26. Capito C, Arnaud A, Hameury F, Fremont B, Lardy H, Leclair MD, Heloury Y. Dysgerminoma and gonadal dysgenesis: the need for a new diagnosis tree for suspected ovarian tumours. *J Pediatr Urol*. 2011 Jun; 7(3): 367–372.
27. Pauls K, Franke FE, Büttner R, Zhou H. Gonadoblastoma: evidence for a stepwise progression to dysgerminoma in a dysgenetic ovary. *Virchows Arch*. 2005 Sep; 447(3): 603–609. Epub 2005 Jun 21.
28. Cheng L, Roth LM, Zhang S, Wang M, Morton MJ, Zheng W, Abdul Karim FW, Montironi R, Lopez-Beltran A. KIT gene mutation and amplification in dysgerminoma of the ovary. *Cancer* 2011 May 15; 117(10): 2096–2103.

29. Cossu-Rocca P, Zhang S, Roth LM, Eble JN, Zheng W, Karim FW, Michael H, Emerson RE, Jones TD, Hattab EM, Cheng L. Chromosome 12p abnormalities in dysgerminoma of the ovary: a FISH analysis. *Mod Pathol*. 2006 Apr; 19(4): 611–615.

30. A L Husaini H, Soudy H, El Din Darwish A, Ahmed M, Eltigani A, A L Mubarak M, Sabaa AA, Edesa W, A L-Tweige-

ri T, Al-Badawi IA. Pure dysgerminoma of the ovary: a single institutional experience of 65 patients. *Med Oncol*. 2012 Dec; 29(4): 2944–2948.

31. Vicus D, Beiner ME, Klachook S, Le LW, Laframboise S, Mackay H. Pure dysgerminoma of the ovary 35 years on: a single institutional experience. *Gynecol Oncol*. 2010 Apr; 117(1): 23–26.